Refer to: Robb LG: Severe vasospasm following ergot administration. West J Med 123:231-235, Sep 1975

Severe Vasospasm Following Ergot Administration

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COMPOUNDS CONTAINING ERGOT are used frequently in the treatment of migraine cephalgia. Ergot is also commonly used in the treatment of postpartum uterine hemorrhage, as well as in uterine subinvolution. The purpose of this paper is to present a case involving a young woman with a history of Raynaud's disease, and the events which followed administration of a single dose of a compound containing ergot.

Ergot alkaloids can exert toxic effects on both the vascular and nervous systems. Since 1930, there have been 41 cases reported of severe vascular effects in patients following administration of ergot compounds.[1-32] Thirty-four (83 percent) of the patients were under 45 years of age and most of them were women (78 percent), as shown in Table 1. In none was a secure diagnosis of preexisting vasospastic disease reported. In only one had a single dose of ergot compound been given, as in our case.

Report of a Case

A 34-year-old woman was first admitted to Hollywood Presbyterian Medical Center with complaint of severe pain and tenderness of the distal right index finger. The finger was found to be cyanotic. Eight years previously, the patient had been told that she had Raynaud's disease. The major finding, at that time, was mottling of the lower extremities, especially in cold weather. The patient was advised to stop smoking; however, this advice was not followed. The changes in the finger were noted six weeks before admission, following an emotionally traumatic incident. Sensation in the finger was intermittently numb or burning. Color changes varied from pale to grey. There was moderate improvement following administration of vasodilating drugs.

On examination, the distal phalanx was seen to be cyanotic, no digital pulses were present and the skin temperature of the digit was 25°C (77°F). The only other significant findings were mottling of the lower extremities and a suggestion of digital clubbing. Skin temperature measurement and impedence plethysmography were carried out. Impedence pulses in the arms showed substantial abnormalities in pulse contour (Figure 1a). The right arm pulse wave appeared damped. There was substantial reduction in ejection velocity and prolongation of pulse duration in the forearm and at the wrist. Skin temperature suggested vasoconstriction.

In order to evaluate vasoconstriction response (Figure 2), ice water submergence was carried out. The legs had pronounced changes in tempera-

TABLE 1—*Reported Cases of Ergot Induced Ischemia*

Reported by	*Number of Cases*	*Sex*	*Age*	*Year*
Antoine[1]	1	F	21	1930
Gould, Price, Ginsberg[2]	1	F	52	1936
Yater, Cahill[3]	1	M	64	1936
Fairbairn[4]	2	M, F	52, 64	1958
Cameron, French[5]	1	F	45	1960
Young, Humphries[6]	1	F	42	1960
Johnson[7]	2	F	34, 35	1961
Ureles, Rob[8]	1	M	36	1963
Bross, et al[9]	1	F	20	1963
Cranley, et al[10]	1	F	30	1963
Kramer, Hecker, Lewis[11]	1	F	54	1965
Engle, Silvertssen[12]	2	F	39, 25	1965
Johnson[13]	1	F	44	1966
Glazer, Myers, Davies[14]	1	M	33	1966
Tator, Heimbecker[15]	1	M	52	1966
Katz, Massry[16]	1	F	33	1966
Fagerberg, Jonulf, Sandberg[17]	1	F	42	1967
Ahlgren, et al[18]	1	F	68	1968
Haynes, Davis[19]	1	F	38	1968
Bertho, Ratte, Joan[20]	1	F	62	1969
Sutton, Preston[21]	2	M, F	33, 29	1970
Felix, Carroll[22]	1	F	39	1970
Dominic, Lysight[23]	1	F	18	1970
Fedotin, Hartman[24]	1	F	40	1970
Yao, Goodwin[25]	1	F	24	1970
Syme[26]	1	F	28	1971
Bagby, Cooper[27]	2	F	42, 59	1972
Manachem, Eger[28]	1	M	36	1972
McLoughlin, Sanders[29]	1	F	39	1972
Hessen, Kromann-Anderson, Madsen[30]	5	F	31, 33, 34, 40, 41	1972
Richter, Banker[31]	1	F	39	1973
Carl, Goldberg et al[32]	1	F	50	1974

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Submitted December 23, 1974.

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ture induced by the cold. The decrease in temperature in the thighs was 1.4°C, calves 1.6°C, ankles 1.8°C, great toes 8.3°C, middle and small toes 7.4°C. Significant decline in skin temperature occurred in the entire right arm with minor temperature decrease in the left. Cigarette smoking produced negligible change in the skin temperature from −0.1°C proximally to −1.2°C distally, after cigarette use.

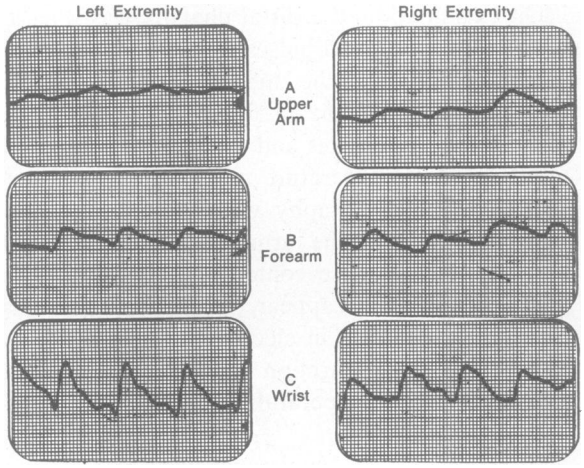

Figure 1.—Impedence pulses in arm. Pulse contours are greatly diminished. The right arm pulse wave is damped. Ejection velocity is reduced and the pulse duration is prolonged.

The presumptive diagnosis of Raynaud's disease was made and the patient was given a cervicothoracic (stellate) ganglion chemical sympathetic block on the right. There was immediate reversion of cyanosis and relief of pain and tenderness. Skin temperature increased (Figure 3) and on plethysmography pronounced improvement was noted (Figure 4). This effect persisted longer than the duration of the block. The patient was discharged as improved, with no onycho cyanosis and only minimal tenderness in the distal phalanx.

Two years later she was admitted again with severe pain, cramping and icy coolness of both legs and the right arm. One week previously, the patient had been treated for menorrhagia by a physician at an outside medical clinic. An intramuscular injection of ergotrate had been administered, which caused extremity pain. The pain increased in intensity, requiring admission to the hospital.

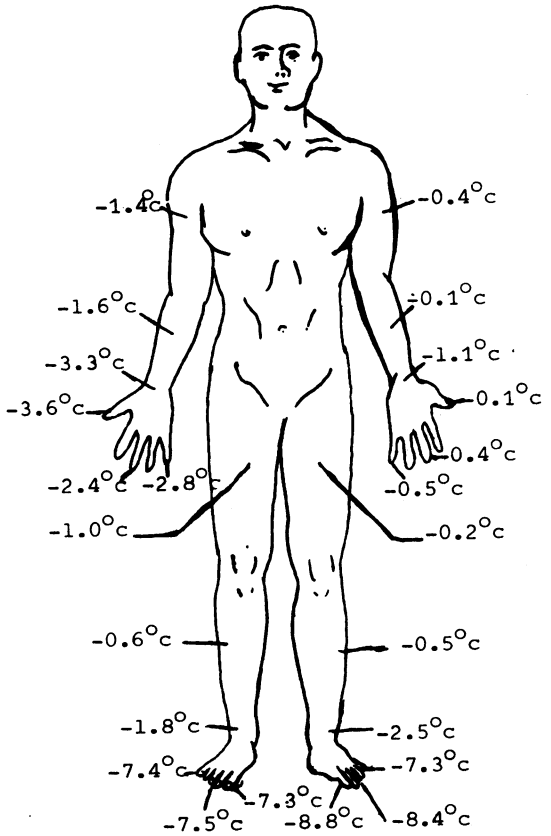

Figure 2.—Ice water emergence for evaluation of vasoreactivity. Temperature change is noted at various sites.

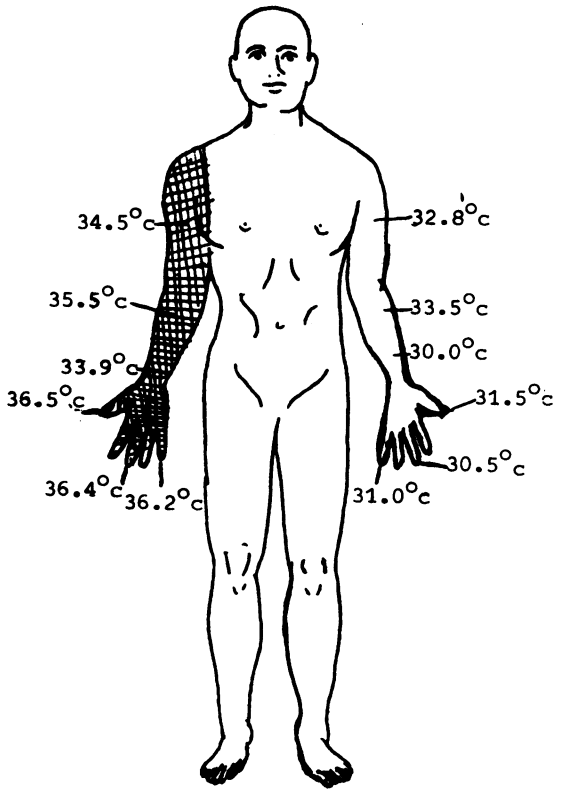

Figure 3.—Cervicothoracic (stellate) ganglion block on right. Increase in skin temperature from blocked to nonblocked extremity is shown.

Administration of vasodilating drugs and tranquilizers did not appear to alter the progression of the vasospasm. The extremities were found to be extremely cold; the color was plethoric proximally to cyanotic distally. The veins were collapsed and could not be filled by the usual measures. The peripheral arterial pulsations were all palpable, but notably diminished. The dorsalis pedis pulse was absent.

A right cervicothoracic chemical sympathetic block (Stellate ganglion) was carried out with bupivicaine 0.25 percent (Marcaine®), a new long-acting local anesthetic. The block resulted in immediate pronounced venodilatation and relief of arterial spasm. The skin temperature increased and the pain was relieved. A lumbar epidural injection of bupivicaine 0.25 percent was given to effect a chemical sympathectomy of the legs. This blockade was continued by insertion of a teflon catheter into the epidural space. Intermittent doses of the local anesthetic were required every six hours to relieve the spasm, afford vasodilatation and relieve pain. The legs were warm to the touch and did not cause discomfort, and sensation was preserved. The patient was capable of full motor function, including walking. The arterial pulsations were subjectively felt to have increased. The epidural catheter was removed in 24 hours.

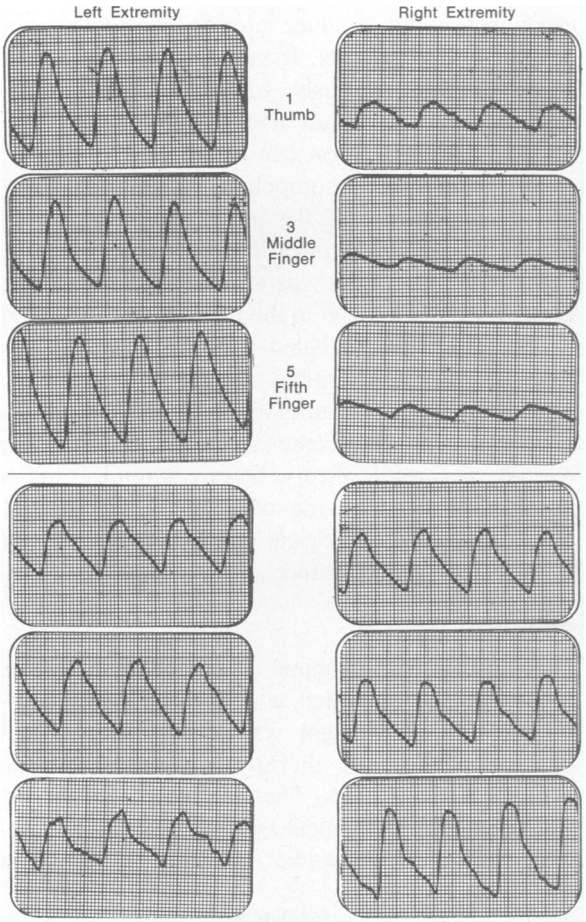

Figure 4.—Upper, Preblock plethysmogram in upper extremities. Digital pulses show diminished contour on the right. **Lower,** Postblock plethysmogram shows dramatic improvement. The pulse contour has returned to normal. Amplitude in the fifth finger is even greater in the right.

Two days following this removal, there was resurgence of symptoms in the left leg and right arm. The stellate ganglion blockade and the continuous lumbar epidural was once again administered, with excellent relief. The patient was discharged 24 hours later, improved.

Comment

To the best of our knowledge, there are no reported cases of ergot administration in patients with Raynaud's disease. Perhaps the cases of reported hypersensitivity or innate sensitivity to ergot are subclinical cases of Raynaud's disease. Other undiagnosed vasoreactive disorders might become evident after the administration of vasospasm-provoking agents.

There are several cases in the literature which illustrate the vasospastic danger after ergot administration. In one, there was severe gangrene of the legs following ergotrate given orally for metrorrhagia in a 20-year-old patient.[9] In another case, severe disability occurred in a 30-year-old nurse, following administration of ergotamine tartrate (Cafergot®) for headaches.[10] This led to four-extremity gangrene, which was resistant to papavarine, tolazoline and heparin. Sympathetic blockade was withheld because the physician believed that "this type of vasospasm was not neurogenic," and would not respond. General anesthesia given for debridement and vascular exploration did not alter the vasospastic consequences.

In many of the cases, the ischemia was resistant to drug therapy; one patient reportedly responded to spinal anesthesia.[13] Besides drug therapy, patients have been treated with various types of sympathetic affector ablation. These include chemical blockades by spinal anesthesia,[13,23,29] single dose epidural or continuous epidural anesthesia,[18,28,29] stellate ganglion blockade[11,15,18] and paravertebral sympathetic blockade.[9,12] Two cases were treated with periarterial sympathectomy[6,20] and two others by surgical sympathectomy.[6]

The effects of ergot in low dosages can be toxic in patients with liver disease.[2,3] One such case re-

ported is that of a 23-year-old woman who was given ergotamine tartrate (Gynergen®) 1 mg three times a day for five days.[16] In the interim, infectious hepatitis developed. Intense vasoconstriction of the small and medium-sized arterioles occurred with local thrombus formation. The liver is the major site of detoxification of this substance, and normally tolerated doses may lead to ergot poisoning when abnormal hepatocellular function exists. This is the reason that ergot compounds are no longer used for the treatment of pruritus associated with jaundice.

Therapeutic doses of ergotamine tartrate (Cafergot®) were given to two young women who had a possible "predisposing hypersensitivity and who developed arterial insufficiency." Sympathetic blocks were reportedly helpful by increasing skin temperature, but otherwise were of "questionable benefit." An "innate sensitivity" was given as the cause of these two cases reported in the *British Medical Journal*.[25]

The classic description of Raynaud was of a disorder in which pallor, cyanosis and rubor of the distal portion of the extremities occurred. If this is associated with another disease (such as scleroderma, lupus erythematosis, rheumatoid arthritis, arteriosclerosis obliterans or thromboangitis obliterans), it is known as Raynaud's phenomenon.

All the criteria in the Gifford and Hines study[33] were present in our patient: (1) there were episodes of pallor, cyanosis and rubor precipitated by cold or emotion; (2) symptoms were bilateral; (3) gangrene was absent or of a minimal degree, limited to the distal cutaneous surfaces; (4) no underlying cause could be found for the preexisting vasospastic episodes, and (5) duration of the symptoms was two years or longer. In addition, the disease is five times more common in women than in men.

The cause of the disease is as yet unknown. A mechanism that has been proposed is digital artery hypersensitivity to vasomotor effects of nervous system hyperactivity. High blood viscosity and elevated plasma fibrinogen concentration have been found in a large percentage of these patients.[34] The significance of this has not been explored.

The mechanism causing pallor is precapillary arteriolarspasm and the reduction of red cells in cutaneous capillaries. Cyanosis is due to stasis of deoxygenated blood in the skin capillaries. Postcapillary constriction allows the stasis to occur. When there is reactive vascular dilatation, the oxygenated blood circulates to the vessels causing the characteristic rubor. This may be due to the vessel wall being affected by anerobic metabolic products (such as lactate, pyruvate and the like) following the initial period.

In Raynaud's disease, the prognosis is usually excellent. Ischemia of a major portion of a limb allegedly never occurs unless, of course, other factors are present. Amputation has been reported in fewer than 0.4 percent of the cases.[33] Frank tissue hypoxia may ensue whenever a vasoconstrictor is used in a patient in whom there is a propensity for vasospasm.[33,34] The vasospastic potential in these "hypersensitive" patients is so profound that a single dose may eventuate into severe consequences.

It is well known that norepinephrine, epinephrine and nicotine synergize the vasoconstrictor activity of ergot. Parenteral administration of ergot is used to produce uterine contractions in postparturient patients. If vasopressors have been administered previously for hypotension, constriction of major organ arterial blood supply and disastrous hypertension can occur.

Physicians using compounds containing ergot are often unaware of the potentially severe consequences of its application in some patients, especially those with vasospastic disorders. The underlying mechanism in the previously mentioned cases, which were labeled with drug hypersensitivity or so-called innate sensitivity, may have been subclinical or undiagnosed cases of Raynaud's disease. Remembering that it is important to take a careful history before administering a drug, as well as having complete knowledge of the drug's pharmacological effects, should prevent this type of misadventure.

Summary

A 34-year-old woman presented with severe menorrhagia, for which a single dose of a compound containing ergot was administered. As a consequence of the therapy, severe vasospastic symptoms developed. The vascular insufficiency was relieved by chemical sympathectomy by lumbar and cervicothoracic sympathetic ganglion blockade.

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Management of Sleep Disorders in the Depressed Patient

What we tend to do with our severely depressed patients is either give them an antidepressant late in the day or give them a single dose of chlorpromazine (Thorazine®) or thioridazine (Mellaril®), 50 or even 100 mg if that turns out to be necessary, at bedtime. A point of fact—the tricyclics do a very good job of improving sleep and they do it fairly rapidly; it is one of their earliest benefits, long before the mood begins to improve, if it does. You might consider, if you are going to put your patient on amitriptyline (Elavil®), for example, that you give most of the dose around bedtime. The other thing is to tell him that his sleep will improve shortly. People can stand a lot of discomfort if they have some reason to think things will get better.

—MERLIN H. JOHNSON, MD, *Seattle*
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